MATHEMATICAL MODEL OF THE EFFECTS OF MECHANICAL VIBRATION ON CROSSBRIDGE KINETICS IN CARDIAC MUSCLE

HIDEYUKI HONDA, M.D., YOSHIRO KOIWA, M.D.
AND TAMOTSU TAKISHIMA, M.D.

We previously reported that the application of an external mechanical vibration to the epicardial surface caused a vibration-induced-depression (VID) of left ventricular (LV) function. The magnitude of the VID of peak LV pressure increased as either the amplitude or the frequency of the vibration increased. When LV contractility was altered by the administration of propranolol or by continuous infusion of dobutamine, the magnitude of the VID of peak LV pressure was inversely correlated with LV contractility. These characteristics were observed in open-chest and isolated canine preparations.

In the present study, we constructed a muscle model to obtain a theoretical explanation for these effects. This model was first proposed by Gray, Gonda and Cheung, and has been extended in this report to explain twitch tension. This new, improved model is able to explain twitch tension and the effects of external vibration on twitch contraction semi-quantitatively. The successful predictions of the this model support the idea that external vibration directly affects contractile protein and modulates crossbridge kinetics.

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WE previously reported that the application of a sinusoidal external mechanical vibration to the left ventricular (LV) epicardial surface induced a depression of the LV cardiac performance (VID)^{1–4}. We speculated that mechanical vibration affected contractile protein and reduced the developed tension. However, it was unclear whether the external mechanical vibration had a direct effect on the contractile apparatus and whether the effect of vibration could be interpreted as a behavior of crossbridge kinetics. These questions led us to establish a theoretical explanation of the effects of vibration on crossbridge kinetics during

twitch contraction. In this study, we propose a theoretical model which can explain crossbridge kinetics during twitch contraction and examined whether this model could explain the effects of vibration on twitch tension.

Some of the experimental results of this study have been reported elsewhere^{1–4}. The characteristics of the effects of vibration on the magnitude of VID are as follows:

In both open-chest and isolated canine preparations, the magnitude of the VID of peak LV pressure increases with an increase of either the amplitude or the frequency of the vibration. Fig. 1 shows a typical example of the relationship between either the frequency or the amplitude of the vibration and the magnitude of the VID of peak LV pressure. Both relationships can be depicted on

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The First Department of Internal Medicine Tohoku University School of Medicine 1-1 Seiryō-Machi Aoba-ku Sendai, Japan

Mailing address: Hideyuki Honda., The First Department of Internal Medicine Tohoku University School of Medicine 1-1 Seiryō-Machi Aoba-ku Sendai 980, Japan

Fig.1. Typical example of the relationships between either the amplitude (open circles) or the frequency (closed circles) of the sinusoidal external mechanical vibration and the magnitude of the VID of peak LV pressure in an isolated canine preparation. The external vibration was applied perpendicularly to the anterior epicardium of cross-circulated isovolumic canine LV under constant rate pacing (90 bpm) and coronary flow (80–100 ml/min/100 g LV). LV volume was fixed at 30 ml, so that peak LV pressure was approximately 100 mmHg. Initially, a mechanical vibration of 50 Hz was applied, and the amplitude was increased in a stepwise manner from 0.13 mm to 1.3 mm at 0.13 mm increments, with interposing quiescent periods (without vibration) of approximately 30 sec. Next, vibration with an amplitude of 1.3 mm was applied, and the frequency was increased in a stepwise manner from 20 to 80 Hz at an increment of 10 Hz, with a similar interposition as in the amplitude scanning.

the same curve. This result suggests that the frequency and the amplitude of the vibration affect the magnitude of the VID similarly.

The magnitude of the VID also depends on myocardial contractility. Fig. 2 shows an example of an open-chest canine preparation. Under the control (no drug) condition, little or no change in LV pressure was induced by external vibration (Fig. 2, upper panel). However, at both 1.5 mg and 4.0 mg of propranolol, peak LV pressure was depressed following the onset of vibration, and

Fig.2. The response of left ventricular pressure to an external vibration in an open-chest canine preparation. From top to bottom are control, propranolol 1.5 mg and propranolol 4.0 mg. A beat just before the onset of vibration (50 Hz, 2 mm-amplitude) is shown to the left of each tracing. The 2 beats before the termination of vibration and the next 2 beats under quiescent conditions are shown. The vibration signal is displayed above each LVP. Reproduced from Koiwa et al¹ with permission of the publisher.

recovered immediately to the quiescent level, i.e., pre-vibration, when the vibration was discontinued (Fig. 2, center panel). The VID of peak LV pressure with 4.0 mg was greater than that with 1.5 mg propranolol. LV end-diastolic pressure in the quiescent condition with propranolol up to 4.5 mg did not differ from that of the control (not shown).

Fig. 3 shows the relationship between the magnitude of the VID and $E_{\max}$ in an isolated canine preparation. The magnitude of the VID of peak LV pressure correlated with $E_{\max}$ ($r = -0.72 \sim -0.99$). Both the VID of peak LV pressure and $E_{\max}$ changed significantly upon infusion of dobutamine, as compared to the control condition ($p < 0.05$).

METHODS

We based our model on that proposed by Gray, Gonda and Cheung⁵⁻⁷ who postulated seven crossbridge states in the contraction cycle, which can be reduced to four basic states (attached force-producing state, attached non-force-producing state, de-

Fig. 3. The relationship between E_{max} and the magnitude of the VID of peak LV pressure in four isolated preparations.

Sinusoidal vibration (50 Hz, 2 mm-amplitude) was applied perpendicularly to the anterior epicardium of cross-circulated isovolumic canine LV under constant rate pacing (90 bpm) and coronary flow rate (80–100 ml/min/100 g LV). LV volume was altered at increments of 1 ml from 0 to 30 ml. LV volume and the VID of peak LV pressure were measured repeatedly while various doses of dobutamine were continuously infused into the coronary circulation to produce changes in myocardial contractility. LV contractility was estimated by E_{max} , which was determined in the quiescent, pre-vibration state by linear regression of peak LV pressure at different LV volumes. There is a significant relationship between E_{max} and the magnitude of the VID. Reproduced from Koiwa et al⁴ with permission of the publisher.

tached state (1) and detached state (2); Fig. 4). The number of crossbridges in the attached force-producing state is proportionate to the developed tension. The reactions proceed in the directions indicated by the arrows in Fig. 4. The reaction rate constants are given as k_1V , k_2 , ... etc. Some of the rate constants include a shortening velocity, V . Gray and Gonda constructed a quantum mechanical formalism on of the contraction cycle and concluded that some processes are affected by the shortening velocity of muscle^{5–10}. They introduced velocity de-

pendency into some of the reaction processes and showed that their model could predict the force-velocity relationship and the dynamic properties of muscle when sinusoidal length perturbation was applied^{7–10}. Therefore, although it is not the most recent model, we selected their model for our simulation. Their original model was limited to either the steady state or a tetanic condition. Thus, we extended this model so that it can explain twitch tension. The key extension is achieved by introducing calcium dependency into process “ k_2 ” of the contrac-

Fig.4. Notations of the state.

N_0 : attached force-producing state. N_1 : detached state (1). N_2 : attached non-force-producing state. N_3 : detached state (2). The value of each N indicates the ratio of crossbridges in that state to the total number of crossbridges. k_1V , k_2 , k_3 , k_4V , k_5 and k_6 indicate rate constants of the respective processes. V represents the shortening velocity of muscle.

TABLE I KINETIC RATE CONSTANTS IN GRAY'S MODEL AND IN OUR STUDY

	Gray et al.	our study
k_1V	66.7	66.7
k_2	9.09	calculated from equation (1)
k_3	0.99	0.99
k_4V	66	calculated from equation (2)
k_5	0.9	0.9
k_6	9	9

tion cycle. The other processes (k_1 , k_3 , ...) cannot satisfy the requirement that almost all of the crossbridges are attached during relaxation (calcium concentration is very low) and detached during full contraction. The only process that can provide this condition is " k_2 ". If $N_0(pCa)$ is defined as the relative number of attached force-producing crossbridges at pCa , then $N_0(pCa)$ is proportional to relative tension and is a function of pCa expressed as a tension- pCa curve.¹¹ The value of k_2 at pCa is calculated as

$$k_2 = k_1 (k_3 + k_5 + k_4V) / k_4 (1/N_0(pCa) - 1 - k_1(1 + k_5/k_6)k_4) \quad (1)$$

(See Appendix A for details). k_4V includes the myosin ATPase process. We approximated the pCa dependency of k_4 (or ATPase activity) by using the results of Onoyama and Ohtuska¹²

$$k_4 = 444667 \frac{\ln \frac{[Ca^{2+}]}{10^{-7}}}{50} + 222333 \quad (2)$$

$$(10^{-7} \leq [Ca^{2+}] \leq 5 \times 10^{-6})$$

Each rate constant is expressed as a constant (k_1 , k_3 , k_5 and k_6) or a function of pCa (k_2 and k_4), as shown in Table I. Consequently, when the time course of the calcium concentration is expressed as a function of time, each rate constant is expressed as a constant (k_1 , k_3 , k_5 and k_6) or as a function of either calcium concentration or time (k_2 and k_4). Therefore, we can calculate the rate of change for each N at every time (see Appendix B for details) and then follow the time course of each N (Fig. 5).

The time course of the transient Ca^{2+} and tension was consistent with the results of Housmans et al.¹³ and Allen et al.¹⁴ To simulate the effects of sinusoidal length perturbation, we changed the shortening velocity V to $V_0 + V_v \sin \omega t$. First, we changed

Fig. 5. Schematic illustration of the calculations used to follow the time course of each N . process 1: The time course of $pCa(t)$ is given. At the beginning of the simulation ($t=0$), we can obtain the initial value of each N by solving the simultaneous equations (7)–(10) in Appendix A. process 2: The change in each N during the time interval Δt is calculated using the equations (12)–(15) in Appendix B. process 3: The value of each N at $t=t+\Delta t$ is calculated using equations (16)–(19) in Appendix B. By repeating process 2 and process 3, we can obtain the value of each N at $t=0$, Δt , $2\Delta t$, $3\Delta t$, ..., and thus follow the time course of each N .

both the amplitude and the frequency of the length perturbation and calculated maximum N_0 . We then altered both ATPase activity and peak Ca^{2+} concentration simultaneously and examined the effects of length perturbation.

Fig. 6. The time course of calcium concentration (broken line), the computed time course of N_0 (solid line) and the experimental tension trace (open circles; the calcium concentration and tension trace are taken from Housmans et al.¹³), assuming that resting and peak Ca^{2+} concentrations are 0.1 and 5 μM , respectively. We selected the shortening velocity so that the calculation of N_0 provides the best fit to the experimental time course of tension. The trace of tension was superimposed with its peak equal to the peak N_0 .

RESULTS

Fig. 6 shows an example of the calculation. The calculated time course of N_0 without vibration during twitch contraction shows a good fit to that of the observed relative tension.

In all cases, the maximum N_0 with a sinusoidal length perturbation is smaller than that without a perturbation. We then examined the relationship between either the frequency or the amplitude of the length perturbation and the decrease of in the maximum N_0 ($-\Delta N_0 \text{ max}$) of the calculated tension. Fig. 7 shows the calculated relationship between either the amplitude or the frequency of the length perturbation and the reduction in the maximum N_0 . Both relationships can be placed on the same curve. As either the amplitude or the frequency increases, $-\Delta N_0 \text{ max}$ increases.

Fig. 8 shows the calculated relationship between ATPase activity, peak Ca^{2+} concentration and the decrease in the maximum N_0 caused by vibration. When both ATPase activity and peak Ca^{2+} concentration decrease simultaneously, the decrease in $N_0 \text{ max}$ increases.

Fig. 7. The calculated relationship between either the amplitude or the frequency of the length perturbation and the reduction in maximum N_0 ($-\Delta N_0 \text{ max}$). In the case of amplitude scanning, the frequency was fixed at 50 Hz and the amplitude was increased to 1% of the sarcomere length. In the case of frequency scanning, the amplitude was fixed at 0.1 % of the sarcomere length, and the frequency was increased up to 500 Hz. The calcium transient is the same as that in Fig. 6.

Note that the "amplitude" in Fig. 1 refers to that of the external mechanical vibration, while the "amplitude" in this figure refers that of the sinusoidal length perturbation of the myocardium. Thus, the former "amplitude" can not be compared directly to the latter "amplitude".

DISCUSSION

External Mechanical Vibration and Sinusoidal Length Perturbation Inhibit the Performance of the Cardiac Muscle

Vukas et al examined the effects of both the frequency and the amplitude of an external vibration on LV performance in open-chest, isolated heart¹⁵ and papillary muscle preparations¹⁶. They showed that the magnitude of the depression of LV performance or the developed tension of twitch contraction decreased with an increase in either the frequency or the amplitude of the vibration, which are similar to the results in our experiments. In addition, we have shown that the effects of vibration depend on myocardial contractility. In the open-chest canine preparation, no alterations in heart rate, coronary flow rate, end-diastolic LV pressure or vascular resistance were observed. Thus, the most probable cause explanation of the de-

Fig. 8. The calculated relationship between ATPase activity and peak Ca^{2+} concentration, and the VID of peak N_0 caused by sinusoidal length perturbation. We assumed that both ATPase activity and peak Ca^{2+} concentration changed simultaneously. The amplitude of the length perturbation is 0.1% of the sarcomere length and the frequency is 50 Hz.

pression of LV pressure due to external vibration is that the vibration affects the force-producing apparatus and reduces the developed tension.

External Vibration May Induce Sarcomere Length Perturbation

We planted pairs of ultrasonic crystals at various sites on the LV wall to measure segment length. When external mechanical vibration was applied to the epicardial surface, sinusoidal length changes synchronous with the external vibration were observed throughout the LV wall, as well as in epicardium near the site at which the external vibration was applied. The amplitude of the changes in the segment length increased with an increase in the amplitude of the external vibration, although this relationship appeared to be non-linear. Vukas et al showed that changes in the sinusoidal length reduced the developed tension of the twitch contraction in a papillary muscle preparation¹⁶. In tetanized muscle, the tension was suppressed as either the frequency or the amplitude of the length perturbation increased^{17,18}. These results suggest that external mechanical vibration induces a length perturbation in the myofibrils of the LV wall, and this length perturbation reduces the developed tension.

Possible Role of the Velocity of Length Perturbation on VID

The present experiment showed that the relationship between the amplitude and the VID of peak LV pressure, and that between the frequency and the VID of peak LV pressure can be put placed on the same curve. This suggests that the frequency and the amplitude of the length perturbation affect the VID in the same manner. If the sinusoidal change of in muscle length is expressed as $L = L_0 + A \sin \omega t$ (A : amplitude of length perturbation), the shortening velocity can be expressed as $dL/dt = V = A \omega \cos \omega t$. Thus, the shortening velocity of length perturbation is proportional to both the amplitude and the frequency of the length perturbation, which shows that amplitude and frequency may affect shortening velocity in the same way. The present experimental result that the frequency affects the magnitude of the VID in the same manner as the amplitude strongly supports the idea that the VID is affected by the velocity of length perturbation, which is consistent with the basic assumption of the model used in this study.

Fig. 1 shows that the VID of peak LV pressure increases approximately in proportion to either the amplitude or the frequency of the external vibration if the VID of peak LV pressure is less than 15%. Fig. 7 shows that $-\Delta N_0 \text{ max}$ increases approximately in proportion to either the amplitude or the frequency of the sinusoidal length perturbation if $-\Delta N_0 \text{ max}$ is less than approximately 20%. In addition, the theoretical estimates of the reduction of tension produced by length perturbation (Fig. 7) were very similar to those reported by Vukas et al.¹⁶ although our theoretical simulations somewhat overestimated the effects of vibration. These results indicate that the model used in this study provides a semi-quantitative prediction of the effect of length perturbation.

Possible Mechanism of Contractility Dependency of VID

It is generally accepted that when a sudden change in muscle length alters the magnitude of tetanic tension, its recovery reflects crossbridge cycling.¹⁹ When crossbridge cycling is inhibited at some process, its recovery is retarded, probably because the number of crossbridges which return to the force-pro-

ducing state decreases.²⁰ Although this experiment involves tetanized muscle, a similar phenomenon may occur during twitch contraction. Sinusoidal length perturbation is considered to be a repeated sudden change in length. This leads to the speculation that, if the cycling rate is reduced for whatever reason, the magnitude of the VID will increase. One purpose of this study was to examine this hypothesis through a simulation, which proved showed that the VID of myocardial twitch contraction was depended on contractility.

Role of β -Agonist and Antagonist

In both the open-chest and isolated canine preparations, when the myocardial contractility was altered by either β -agonist or β -antagonist, the depression of peak LV pressure was inversely correlated with myocardial contractility (Fig. 3). β -agonist increases both the peak Ca^{2+} concentration²¹ and the crossbridge cycling rate.^{22,23} Our simulations showed that when both ATPase activity and peak Ca^{2+} concentration decreased simultaneously, the depression of tension induced by length perturbation increased, and that neither ATPase activity nor peak Ca^{2+} concentration alone caused such a similar change in tension (not shown).

β -agonist decreases myofilament Ca^{2+} sensitivity.²⁴ Since it is unclear which process in the present model is responsible for Ca^{2+} sensitivity, we did not simulate the effects of Ca^{2+} sensitivity on the VID of peak LV pressure. We previously reported that the VID of peak LV pressure increased non-linearly as LV end-diastolic volume increased in an isolated canine preparation.² This showed that VID increased with an increase in sarcomere length. Since an elongation of sarcomere length induces an increase in Ca^{2+} sensitivity,²⁵ the alteration of Ca^{2+} sensitivity induced by β -blockers might play an important role in the change of the magnitude of the VID.

Local Myocardial Function and Total LV Function

Experiments have shown that the magnitude of the VID of peak LV pressure greatly depends on LV contractility. On the other hand, the simulation in this study showed that the peak twitch tension reduced de-

clined nearly 20% with vibration. This discrepancy appears to suggest that the simulation unable to explain the experimental results. We previously reported another simulation study which related local LV wall myocardial contractility to total LV function.^{26,27} That simulation was based on a model proposed by Beyar and Sideman²⁸ with some modifications. In that study, we showed that if the external vibration reduced myocardial twitch tension, LV function (peak LV pressure, stroke work, ejection fraction, etc.) also decreased. We examined three potential relationships between the reduction in myocardial wall tension and basic myocardial contractility (case 1, the reduction in wall tension induced by vibration shows a positive linear correlation with myocardial contractility; case 2, the reduction of in wall tension is independent of myocardial contractility; and case 3, the reduction in wall tension shows a negative linear correlation with myocardial contractility). The simulation showed that in case 3, the calculation fitted semi-quantitatively very well to the experimental results. In case 2, the agreement between the simulation and the experiment was inferior to that of case 3. The reduction in LV function may depend on contractility, even when the reduction in local myocardial tension is independent of myocardial contractility, due to mechanisms (LV shape, fiber orientation, etc.) which relate local myocardial tension to total LV function.²⁷ The simulation in this study showed that the reduction of in peak tension induced by vibration showed a weak negative dependency on myocardial contractility. These results suggest that this dependency has two potential causes: 1) the magnitude of the vibration-induced reduction in myocardial tension may depend on myocardial contractility; and 2) the mechanisms which relate local myocardial function to total LV function may cause this dependency.

In summary, our model was able to explain the relation between either the frequency or the amplitude of the vibration and the reduction in peak LV pressure. In addition, we were able to simulate the dependency of LV contractility, which was consistent with the experimental results. The magnitude of the VID varies according to LV size, the conditions of the experimental prepara-

tion, and perhaps other factors as well. Although we did not examine all of the factors that might affect the magnitude of the VID of peak LV pressure, the fact that the present model could successfully predict the effects of vibration supports the idea that external vibration directly affects the contractile machinery and reduces the developed tension.

APPENDIX A

The rate equations for each N are

$$\frac{dN_0(pCa)}{dt} = k_4 V N_2(pCa) - k_1 V N_0(pCa) \quad (3)$$

$$\frac{dN_1(pCa)}{dt} = -k_2 N_1(pCa) + k_6 N_3(pCa) + k_3 N_2(pCa) + k_1 N_0(pCa) V \quad (4)$$

$$\frac{dN_2(pCa)}{dt} = k_2 N_1(pCa) - k_3 N_2(pCa) - k_5 N_2(pCa) - k_4 N_2(pCa) V \quad (5)$$

$$\frac{dN_3(pCa)}{dt} = k_5 N_2(pCa) - k_6 N_3(pCa) \quad (6)$$

where $N_0(pCa)$, $N_1(pCa)$, $N_2(pCa)$ and $N_3(pCa)$ indicate the ratio of crossbridges at each state to the total number of crossbridges at pCa. $k_1 V$, k_3 , k_5 and k_6 are constants, and k_2 and k_4 are functions of pCa calculated by equation (1) and equation (2), respectively (Table I).

In a steady state, the change rate of change for each N is zero ($dN_i(pCa)/dt = 0$ for $i = 0, 1, 2, 3$). Thus, we can obtain the following simultaneous equations

$$k_4 V N_2(pCa) - k_1 V N_0(pCa) = 0 \quad (7)$$

$$-k_2 N_1(pCa) + k_6 N_3(pCa) + k_3 N_2(pCa) + k_1 N_0(pCa) V = 0 \quad (8)$$

$$k_2 N_1(pCa) - k_3 N_2(pCa) - k_5 N_2(pCa) - k_4 N_2(pCa) V = 0 \quad (9)$$

$$k_5 N_2(pCa) - k_6 N_3(pCa) = 0 \quad (10)$$

Solving these equations, we can obtain $N_0(pCa)$ as

$$N_0(pCa) = \frac{1}{1 + \frac{k_1(k_3 + k_4 V + k_5)}{k_2 k_4} + \frac{k_1 + k_1 k_5}{k_4 k_6}} \quad (11)$$

where $k_1 V$, k_3 , k_5 and k_6 are constants, and k_4 is given by the equation (2). Therefore the, equation (11) can be transformed as

$$k_2 = k_1 (k_3 + k_5 + k_4 V) / k_4 (1/N_0(pCa) - 1 - k_1 (1 + k_5/k_6) / k_4) \quad (1)$$

APPENDIX B

The rate equations for each N at pCa are

$$\frac{dN_0(pCa)}{dt} = k_4 V N_2(pCa) - k_1 V N_0(pCa) \quad (3)$$

$$\frac{dN_1(pCa)}{dt} = -k_2 N_1(pCa) + k_6 N_3(pCa) + k_3 N_2(pCa) + k_1 N_0(pCa) V \quad (4)$$

$$\frac{dN_2(pCa)}{dt} = k_2 N_1(pCa) - k_3 N_2(pCa) - k_5 N_2(pCa) - k_4 N_2(pCa) V \quad (5)$$

$$\frac{dN_3(pCa)}{dt} = k_5 N_2(pCa) - k_6 N_3(pCa) \quad (6)$$

When the time course of the calcium concentration is given as a function of time, these equations can be expressed as

$$\frac{dN_0(t)}{dt} = k_4 V N_2(t) - k_1 V N_0(t) \quad (3')$$

$$\frac{dN_1(t)}{dt} = -k_2 N_1(t) + k_6 N_3(t) + k_3 N_2(t) + k_1 N_0(t) V \quad (4')$$

$$\frac{dN_2(t)}{dt} = k_2 N_1(t) - k_3 N_2(t) - k_5 N_2(t) - k_4 N_2(t) V \quad (5')$$

$$\frac{dN_3(t)}{dt} = k_5 N_2(t) - k_6 N_3(t) \quad (6')$$

Thus, the change in each N at t ($\Delta N_i(t)$, $i=0, 1, 2, 3$) over a short time interval (Δt) can be expressed as

$$\Delta N_0(t) = (k_4 V N_2(t) - k_1 V N_0(t)) \Delta t \quad (12)$$

$$\Delta N_1(t) = (-k_2 N_1(t) + k_6 N_3(t) + k_3 N_2(t) + k_1 N_0(t) V) \Delta t \quad (13)$$

$$\Delta N_2(t) = (k_2 N_1(t) - k_3 N_2(t) - k_5 N_2(t) - k_4 N_2(t) V) \Delta t \quad (14)$$

$$\Delta N_3(t) = (k_5 N_2(t) - k_6 N_3(t)) \Delta t \quad (15)$$

When the time is $t + \Delta t$, each N can be calculated as

$$N_0(t + \Delta t) = N_0(t) + \Delta N_0(t) \Delta t \quad (16)$$

$$N_1(t + \Delta t) = N_1(t) + \Delta N_1(t) \Delta t \quad (17)$$

$$N_2(t + \Delta t) = N_2(t) + \Delta N_2(t) \Delta t \quad (18)$$

$$N_3(t + \Delta t) = N_3(t) + \Delta N_3(t) \Delta t \quad (19)$$

By repeating this step from $t=0$ to $t=400$ msec with a time interval (Δt) of 1 msec, we can calculate the time course of each N.

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